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## CORRESPONDENCE



## Estrogen Therapy and Coronary-Artery Calcification

**TO THE EDITOR:** In their article on the Women's Health Initiative Coronary-Artery Calcium Study (WHI-CACS), Manson et al. (June 21 issue)<sup>1</sup> provide insight into another mechanism by which estrogen therapy reduces coronary heart disease (CHD) in women who have undergone hysterectomy and who initiate such therapy close to menopause.<sup>2</sup> The authors' findings further support the hypothesis that early initiation of such therapy has a beneficial effect.<sup>3</sup>

For women under the age of 60 years, scientific evidence indicates that estrogen therapy is as efficacious in reducing CHD as are other primary prevention therapies, such as lipid-lowering drugs and aspirin, and is more effective in reducing total mortality.<sup>4</sup> For women in this age group, estrogen therapy has a risk profile that is no greater than that of other medications used for primary prevention of CHD in women.<sup>4</sup> Studies by the WHI, other randomized trials, and observational studies (including the WHI observational

study) show significant trends toward a greater benefit with respect to total mortality and CHD with a longer duration of estrogen therapy.<sup>2,4</sup>

WHI-CACS was similar to the Estrogen in the Prevention of Atherosclerosis Trial<sup>5</sup> in providing mechanistic evidence for a role of estrogen therapy in the prevention of CHD in postmenopausal women. WHI not only has confirmed the known benefits from observational studies but also has clearly shown the relative safety of estrogen therapy under randomized, controlled conditions in women under the age of 60 years (Table 1).<sup>2,4</sup>

**Table 1. Effect of Therapy with Conjugated Equine Estrogen on Major Outcomes in Women under the Age of 60 Years.\***

Event	Estrogen as Compared with Placebo	
	Percent Difference	Absolute Difference in No. of Events per 10,000 Women per Year of Therapy
Death	-29	-11
Coronary heart disease	-37	-11
Stroke	-11	-2
New-onset diabetes mellitus	-12	-14
Bone fracture	-30	-56
Breast cancer†	-18	-8
Venous thromboembolism‡	+37	+4

\* Data are from the Women's Health Initiative.

† The reduction was 33% among women whose compliance with the estrogen-therapy regimen was at least 80% (risk ratio, 0.67; 95% confidence interval, 0.47 to 0.97).

‡ This category includes deep-vein thrombosis and pulmonary embolism.

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Dr. Hodis reports receiving consulting fees from Wyeth. No other potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** With regard to the report by Manson et al. on the effect of estrogen therapy on calcium scores in a subgroup of middle-aged women from the WHI trial,<sup>1</sup> we feel it is somewhat unfortunate to state that the data provide some reassurance that estrogen therapy may not be harmful. Conclusions with regard to clinical outcome should be drawn only from trials that are designed and powered to address clinical events. If a surrogate end point is presented, it should have an established association with a clinical outcome and be obtained in a trial with optimal methodology.

The WHI trial was not designed to address the effect of estrogen on calcium scores, which accounts for the lack of a baseline calcium score and explains why modifiable risk factors (e.g., smoking) and the use of concomitant medication were not routinely scored during follow-up. Moreover, in low-risk subjects, the prognostic effect of calcium scores is far from established.<sup>2,3</sup> In our opinion, the reported effects of estrogen therapy on calcium scores should be considered as hypothesis-generating. We look forward to the clinical follow-up after computed tomography has been performed to provide insight into the possible prognostic value of these findings.

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**TO THE EDITOR:** Manson et al. convincingly show that estrogen-only replacement therapy, when started between the ages of 50 and 59 years in postmenopausal women who have undergone hysterectomy, reduced coronary-artery calcification. This article and the accompanying editorial by Mendelsohn and Karas<sup>1</sup> provide us with valuable arguments when translating evidence into clinical practice. Since bone represents the body's largest storage compartment for calcium, and estrogen-only replacement therapy increased bone mass,<sup>2</sup> the antiresorptive effects of estrogen may have contributed to reduced vascular calcification by reducing the efflux of calcium from bone. Were bone markers or measurements of bone mineral density available for these women, and were such measures correlated with calcification scores?

As the authors mention, the vascular effects of estrogens are complex and occur at multiple levels, including gene expression of bone-related factors.<sup>1</sup> Osteoprotegerin represents an estrogen-responsive cytokine with skeletal and vascular effects,<sup>3</sup> and deletion of this protein in mice leads to osteoporosis and vascular calcification.<sup>4</sup> Were serum osteoprotegerin levels assessed in this study? In our opinion, this cohort represents a pivotal opportunity to shed further light on the mechanisms underlying the osteoporosis-vascular calcification syndrome.

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**THE AUTHORS REPLY:** Hodis and Mack state that for women under the age of 60 years who have undergone hysterectomy, estrogen reduces CHD and is more effective in reducing total mortality than are other primary prevention therapies. Moreover, they assert that the WHI has "clearly shown" the relative safety of estrogen therapy in women under 60. We disagree that the WHI conclusively showed that estrogen therapy reduces either CHD or total mortality in younger women. Although younger women receiving estrogen appeared to have a more favorable balance of benefits and risks than did older women, interaction tests according to age showed only borderline significance.<sup>1</sup>

In addition, it remains unclear whether with prolonged treatment any coronary benefits of estrogen therapy in women under the age of 60 years would persist at older ages, when coronary events become more frequent. We do believe that the WHI findings on estrogen therapy in younger women, combined with the low absolute rates of vascular events in this age group, provide some reassurance to recently menopausal women who are considering hormone therapy for the short-term treatment of menopausal symptoms. However, in light of other risks, we believe that hormone therapy should not be used for the prevention of CHD or other chronic diseases.

We agree with Brouwer and colleagues that conclusions with regard to clinical outcomes should be drawn from trials designed and powered to address clinical events. However, we did not state that the data provide reassurance that estrogen therapy may not be harmful. Indeed, we noted explicitly that "other risks and benefits of treatment must be considered," even though estrogen is "unlikely to have an adverse effect on

the risk of coronary events among women who have recently undergone menopause." However, coronary-artery calcium scores do appear to improve prediction of the risk of CHD, even in asymptomatic persons at relatively low risk for CHD.<sup>2</sup>

Finally, we concur with Hofbauer et al. that the mechanisms underlying the relationship between estrogen and vascular calcification, including the possible role of antiresorptive effects of estrogen, warrant further study. We do not have data on serum osteoprotegerin levels, and we have data on bone mineral density for only a small number of women, so we cannot address the correlations proposed by Hofbauer et al. Notably, a postmortem study of coronary arteries suggested that estrogen therapy was associated with both a smaller plaque area and reduced calcium content.<sup>3</sup> Coronary-artery calcium scores in WHI-CACS were strongly correlated with traditional risk factors for CHD, including smoking, hypertension, hypercholesterolemia, and diabetes, suggesting a strong correlation with atheromatous plaque burden. We hope that future analyses of data from WHI-CACS and other studies will further elucidate the mechanistic basis for the relationships we observed.

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